Age-related dysfunction in mechanotransduction impairs differentiation of human mammary epithelial progenitors.

Journal: Cell Rep

Publication Year: 2014

Authors: Fanny A Pelissier, James C Garbe, Badriprasad Ananthanarayanan, Masaru Miyano, ChunHan Lin, Tiina Jokela, Sanjay Kumar, Martha R Stampfer, James B Lorens, Mark A LaBarge

PubMed link: 24910432

Funding Grants: Interdisciplinary Training in Stem Cell Biology, Engineering and Medicine

Public Summary:
In human mammary gland, differentiation-defective multipotent progenitors (MPPs) accumulate with age, accompanied by a shift in the proportion of daughter myoepithelial and luminal epithelial cells. The molecular composition and tissue elasticity in breast likely plays an instructive role in the differentiation of normal mammary epithelial progenitors, but the effect of age-related changes on breast elasticity is not known. We hypothesized that MPPs accumulate in mammary tissue of older individuals because they do not correctly perceive microenvironmental differentiation cues, and that these age-associated changes make aged breast tissue susceptible to malignant progression. Here we engineered tunable 2D and 3D tissue culture substrata to test the effect of elastic modulus on MPP differentiation. Differentiation patterns of MPP from women aged <30 years were exquisitely responsive to a physiologically relevant range of elastic modulus, whereas MPP from women >55 years were relatively unresponsive to changes in rigidity. Our data suggest that aging phenotypes of mammary epithelia may arise partly because alterations in activation of the Hippo signaling pathway impair microenvironment-directed differentiation and lineage specificity.

Scientific Abstract:
Dysfunctional progenitor and luminal cells with acquired basal cell properties accumulate during human mammary epithelial aging for reasons not understood. Multipotent progenitors from women aged <30 years were exposed to a physiologically relevant range of matrix elastic modulus (stiffness). Increased stiffness causes a differentiation bias towards myoepithelial cells while reducing production of luminal cells and progenitor maintenance. Lineage representation in progenitors from women >55 years is unaffected by physiological stiffness changes. Efficient activation of Hippo pathway transducers YAP and TAZ is required for the modulus-dependent myoepithelial/basal bias in younger progenitors. In older progenitors, YAP and TAZ are activated only when stressed with extraphysiologically stiff matrices, which bias differentiation towards luminal-like phenotypes. In vivo YAP is primarily active in myoepithelia of younger breasts, but localization and activity increases in luminal cells with age. Thus, aging phenotypes of mammary epithelia may arise partly because alterations in Hippo pathway activation impair microenvironment-directed differentiation and lineage specificity.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/age-related-dysfunction-mechanotransduction-impairs-differentiation-human